UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/374,554	08/13/1999	ANDREW W. SHYJAN	MRI-005CP2	3905

959 7590 11/06/2002

LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/06/2002 17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/374,554	Applicant(s) SHYLAN ET AL.	
	Examiner Jeanine A Goldberg	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,6,12,18,21,27,32,33,35 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,6,12,18,21,27,32,33,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed August 16, 2002. Currently, claims 3, 6, 12, 18, 21, 27, 32, 33, 35, 36 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

2. Any objections and rejections not reiterated below are hereby withdrawn in view of applicants arguments or the amendments to the claims.

Maintained Rejections

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 3, 6, 12, 18, 21, 27, 32, 33, 35, 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working

examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Breadth of the Claims

The claims are broadly drawn to methods of determining whether TAXOL cannot be used to reduce the growth of cancer cells, and methods for determining whether or not treatment with TAXOL should be continued in a cancer patient be determining the expression level of BST2.

Guidance and Direction Presented and Working Examples

The specification teaches cancer cell lines are used to determine whether genes and/or ESTs are sensitive or resistant (page 34). These nucleic acids were places upon an Affymetrix GeneChip systems and analyzed with respect to the hybridization patterns and intensities. This appears as though it was used to identify which nucleic acids are expressed in cancer cell lines and what how they were affected by different agents. Example 2, page 40, teaches identification of sensitivity and resistance genes *in vivo*. Each of these studies relates to cisplatin and cyclophosphamide. The specification states, page 41, that "the gene descriptions refer to sequence immobilized on an Affymetrix HUM6000 gene chip and that the names associated with the sequences may not be the actual names of the genes that are hybridizing to the bound probe." On page 44, Example 5, the specification teaches three studies which are directed to TAXOL. Genes are identified which are relatively highly expressed in TAXOL resistant cell lines. The levels of expression in mammary epithelial cell primary cell lines and breast cancer cell lines were compared. Moreover, breast cancer clinical samples which appeared to respond well and poorly to TAXOL were compared.

The state of the Art

BST-2 expression

The art teaches that BST-2 is expressed in human cell lines including those with the origin of hepatoma, bladder cell carcinoma, glioblastoma and cervical cancer carcinoma (Ishikawa et al. Genomics, Vol. 26, pages 527-534, 1995). Ishikawa also illustrates that BST-2 mRNA are expressed in a variety of tissues including pancreas, kidney, skeletal muscle, liver, lung, placenta, brain and heart.

Taxol Screening Methods

The art teaches characterization of taxol-induced apoptosis and altered gene expression in human breast cancer cells (Cheng et al. Cellular Pharmacology, Vol 2, pages 249-257, 1995). Cheng teaches using a PCR-mediated differential screening procedure and Northern analysis, 12 taxol response genes were identified from human breast tumour cell line that are either up- or down-regulated by taxol (abstract, Table 1).

Taxol sensitivity not related to p53 expression levels

Borbe et al (Cancer Chemother Pharmacol. Vol 44, pages 217-227, 1999) teaches an analysis of a panel of 12 human glioma cell lines which revealed no relationship between genetic or functional p53 status and taxol sensitivity. Moreover, Borbe teaches "activity of taxol against malignant glioma cell lines in vitro has been shown in several studies. However, despite the remarkable in vitro potency of taxol, phase II clinical studies of taxol for primary or recurrent malignant gliomas showed no relevant activity" (page 218, col. 1).

As provided in the art, p53 is commonly overexpressed in gliomas. Pykett et al (International J. of Oncology, Vol. 13, No. 2, pages 213-216, August 1998-abstract only) teaches that gliomas are part of a subset of tumors in which overexpresion of p53 protein in the absence of p53 gene mutation has been described.

Cell lines not indicative of Tumors

Dermer *et al.* (Biotechnology Vol. 12, March 1994, p. 320) teach that cell lines are a poor representation of malignancy because they have survived crisis and have adapted an immortal life in culture, and thus has been enabled to survive in its artificial environment. Dermer *et al.* state that "the petri dish cancer is really a poor representation of malignancy, with characteristics profoundly different from the human disease."

Orr et al. (J. of the National Cancer Institute, Vol 92, No. 12, June 21, 2000, pages 987-994) teaches that the normal cells were used to avoid the genetic complexities associated with established cell lines. Orr suggests that cellular studies using normal human cells in which the complexity of the system can be carefully

controlled by the addition of one, two or even more genes associated with cancer development may provide valuable information about how the products of the genes interact with each other and which combinations are critical in regulating chemosensitivity.

Eastham et al. (Int. J. Radiat. Biool. Vol. 77, No. 3, pages 295-302, 2001) teaches that "poor correlation between the different endpoints precludes their use in a clinical setting on primary tumour samples in vitro. It may be that tumour cell lines in vitro are a poor model for tumours in vivo. Studies aimed at assessing assys for measuring tumour radiosensitivity therefore should employ clinical samples. In vitro cell line work should concentrate on unraveling the complex mechanisms involved in determining a radiosensitive or radioresistant phenotype" (page 295, col 1, abstract). Moreover, Eastham teaches that "using cell lines derived from a single tumour type no correlation was found between clonogenic survival and the two different endpoints studied" (page 299, col 2).

Undue experimentation and unpredictability of the art

As a preliminary matter, the specification is confusing as to whether breast cancer patients or ovarian cancer patients were studied on page 50. On page 45, the specification appears to be describing a study which samples breast cancer clinical samples obtained from patients whose breast cancer appeared to respond toTAXOL/cisplatin combination therapy and breast cancer clinical samples which appeared to respond poorly (lines 17-25). The specification further states that the

genes which were identified are provided in Table 11A and 11B. However, on page 50, the specification discusses differential expression of genes in responsive and non-responsive ovarian cancer. The specification discusses ovarian cancer patients who responded both well and poorly were sampled and the results of the genes identified are in Table 11A and 11B (lines 10-20). This appears to be conflicting to the statements on page 46. However, the specification also teaches that the clinical samples were patients undergoing breast cancer therapy (lines 22-24). Therefore, it is unclear what data is provided in Table 11A and 11B.

The problem with the claims, particularly Claim 3 and narrower Claim 18 is the absence of correlation between the resistance gene chosen and any evidence that the gene has a relationship to TAXOL resistance itself. For example, a gene determined as expressed in TAXOL resistance cells may be a gene expressed by all cells. BST-2 appears to be such a gene. As provided in Ishikawa, BST-2 is expressed in pancreas, kidney, skeletal muscle, liver, lung, placenta, brain and heart tissues as well as hepatoma, bladder cell carcinoma, glioblastoma, and cervical cell carcinoma cell lines. So absence of a correlation of BST2 or any of the genes in the Tables provided renders Claim 18 non-enabled because the gene is not evidenced to be a resistance gene. Its differential expression upon exposure to TAXOL may be indicative of apoptosis, for example, and not TAXOL resistance. Over expression alone is not proof of taxol resistance. Under such a notion, Figure 7 of Ishikawa would illustrate, that heart muscle which appear to express BST-2 at higher levels than the kidney would imply that kidney tissue would be TAXOL sensitive whereas heart tissue would be resistant to TAXOL

because BST-2 is over expressed. The specification teaches that for BST-2 three of the four cell lines studied for sensitivity illustrated that expression of BST-2 was present, albeit at lower levels than the two resistant cell lines.

Neither the specification nor the art teaches how to make and use the invention as broadly as claimed. First, cancer cell lines are not indicative of patient samples. The elected BST2 gene appears in Table 9B. Table 9B appears to be a list of genes that are relatively highly expressed in selected relatively TAXOL resistant breast cancer cell lines compared to selected relatively TAXOL sensitive breast cancer cell lines (page 47, lines 33-37). As noted above, the specification does not appear to have studied patient samples from breast cancer individuals. Cancer cell lines have been taught in the art not to be appropriate models for patient samples. The specification fails to provide any evidence that a similar pattern of TAXOL resistance is present in actual tumor tissue from a clinical patient. The expression pattern of BST-2 in cancer cell lines is not sufficient evidence to enable one skilled in the art to determine that this mRNA would necessarily be over-expressed in primary tumor tissue as compared to non-tumor tissue. Borbe teaches, "activity of taxol against malignant glioma cell lines in vitro has been shown in several studies. However, despite the remarkable in vitro potency of taxol, phase II clinical studies of taxol for primary or recurrent malignant gliomas showed no relevant activity" (page 218, col. 1). Borbe thus stands for the proposition that genes, namely p53, shown to be over expressed in glioma cell lines are not associated, and further they are not associated in vivo. Dermer *et al.* (Biotechnology Vol. 12, March 1994, p. 320) teach that cell lines are a poor representation of

malignancy because they have survived crisis and have adapted an immortal life in culture, and thus has been enabled to survive in its artificial environment. Dermer *et al.* state that "the petri dish cancer is really a poor representation of malignancy, with characteristics profoundly different from the human disease." Furthermore, Orr teaches that the normal cells were used to avoid the genetic complexities associated with established cell lines. While the ordinary practitioner in this field is highly skilled, the evidence presented in the specification does not provide even a highly skilled practitioner means to overcome the limitations of evidence derived from cell lines and to make and/or use BST-2 as a method for cancer diagnosis and/or detection with any reliability. As discussed by Dermer *et al.*, Orr et al and Eastham, the level of predictability between the activity of tumor cell lines and actual tumor tissue is very low, and thus practicing this invention would require unreasonable experimentation on the part of the practitioner to further screen actual tumor tissue to test for a connection between BST-2 expression and cancer resistance to TAXOL. In light of the teachings in the prior art, and the general unpredictability concerning the activity of BST-2 in tumor cell lines versus actual tumor tissue, the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Even in the event that the Table 11A was directed to genes which are relatively expressed at a relatively high level in TAXOL/cisplatin resistant clinical samples from breast cancer patients as compared to TAXOL/cisplatin sensitive clinical samples, the study includes an additional agent, namely cisplatin, and also does not contain the BST-

2 gene. Therefore, there is no indication that patient cells treated with TAXOL alone would be indicative of the inability for TAXOL to be used to reduce the growth of cells. The combination of the two drugs may have varying effects on the gene expression such that different results are obtained between samples treated with TAXOL alone and with TAXOL in combination with cisplatin. Furthermore, BST2 does not appear to be among those genes which are identified to be relatively highly expressed in the clinical trials. Therefore, this appears to support the notion that there is no noticeable correlation between cell lines and patient samples. In the event that cell lines and patient samples were similar, the genes which are expressed at a relatively higher level in cell lines should be very similar to those genes identified to be expressed at a relatively higher level in patient samples.

Secondly, different cancers act in different manners. The specification appears to clearly illustrate that different genes are expressed in relatively higher manners for different cancer cell lines. For example, the specification sample colon, breast, ovarian, and melanoma. The genes which appear to be relatively highly expressed in relatively TAXOL resistant cell lines appear to differ between the different cell lines, indicating that not all genes are differentially expressed in different cancer cell lines. For example, determination that BST-2 is relatively highly expressed in breast cancer cell lines does not provide any indication of how this gene functions in any other type of cancer cell lines. The different variety of cancers affect different genes such that the expression of one gene is not indicative of how the gene would act in a different cancer type.

Thirdly, the specification appears to only sample TAXOL resistant cell lines, however does not appear subjecting any cancer cells to TAXOL and assaying for BST2 mRNA expression. Since the mechanisms of TAXOL and how the agent works within cells is unknown, merely using cell lines which are "TAXOL resistant" does not appear to simulate subjecting cells to the TAXOL agent. The TAXOL resistant cells have not been subjected to an agent, namely TAXOL, they are only believed to have some resistance to TAXOL. The studies which involved clinical samples had been subjected to the TAXOL agent and had been subjected to the agent in vivo. There is no indication how cells treated with TAXOL which keep growing respond to expression levels of BST2. The specification teaches sampling cells and assaying for expression of mRNA in vitro. The specification has not provided any teachings with respect to sampling the expression of mRNA in vivo. There is no indication that TAXOL is what causes the different expression patterns of the genes when only TAXOL resistant cells are studied. The specification additionally does not appear to consider that TAXOL affects a gene which is involved in a pathway or cascade which is either upstream or downstream of BST2. Therefore, the apparent relatively high expression of the gene in a TAXOL resistant cell line does not appear to provide correlation to clinical sample which have actually been treated with TAXOL. As stated above, these studies appear to yield different results, therefore, the determination of an in vivo study does not appear to correlate with in vitro studies.

Finally, as clearly admitted and pointed out in the specification, page 41, "the gene descriptions refer to sequence immobilized on an Affymetrix HUM6000 gene chip

and that the names associated with the sequences may not be the actual names of the genes that are hybridizing to the bound probe." Therefore, the specification appears to indicated that the identification of the actual names of the genes may not be truly what was identified. Therefore, without assaying for the true known gene BST2 it is unpredictable that the sequences hybridizing to the bound probe are in fact the nucleic acid sequences of BST2.

Therefore, in order to practice the claimed invention as a whole as broadly as claimed, the skilled artisan would be required to perform extensive additionally experimentation with unpredictable results. The skilled artisan would be required to determine how the gene functions in an environment which is different than the cell lines which were studied in the specification. The skilled artisan would be required to determine how the gene functions with respect to the specific cancer of interest of the patient. Finally, the skilled artisan would be required to determine how the application of TAXOL in vitro differs, if it does, to the application of TAXOL in vivo.

Response to Arguments

The response traverses the rejection. The response asserts that the claims are enabled based upon the teachings in the specification. The response states that the first study which is directed to nucleic acids in table 9B, BST-2 being one of those nucleic acids, is a study of nucleic acid sequences which are relatively highly TAXOL resistant solid tumor cell lines from the NCI 60 cancer cell line series, namely breast cancer cell lines (page 13, 18-19 of response field August 16, 2002). The response asserts that the teachings of Ishikawa are not relevant to the instant inquiry because

Ishikawa merely teaches expression levels in normal tissues. The response asserts that chemotherapeutic agents such as TAXOL operate by inducing apoptosis therefore, if a gene is identified from a sample that when exposed to TAXOL, inhibits apoptosis, by definition it is a TAXOL resistant gene. The specification appears to provide a different definition for resistant genes. The specification teaches that "resistant genes are those genes that are expressed in most or all cell lines that are resistant to treatment with an agent and which are not expressed in cells that are sensitive to treatment with an agent)(page 2 of specification). This argument has been reviewed but is not convincing because the specification fails to expose a sample to TAXOL to determine apoptosis. The specification has only described expression levels in cell lines which are asserted to be TAXOL resistant. Moreover, as noted previously, the specification teaches that for BST-2 three of the four cell lines studied for sensitivity illustrate that expression of BST-2 was present, albeit at lower levels that the two resistant cell lines. Therefore, it is unclear from the specification whether BST-2 can or cannot be used to reduce the growth of breast cancer cells.

The response filed August 16, 2002 (page 15) traverses the rejection as it applies to cell lines. The response submit that tumor cancer cell lines are appropriate and useful model for studying behavior of tumor cells. The response submits Hopfer and Geller as support for their position, however, the references do not say in vitro corresponds to in vivo results. The teachings of Borbe specifically are directed to taxol studies in cancer, therefore, the teachings of Borbe appear to be more relevant to the question of enablement than general teachings of in vitro tumor cells. Applicant's

arguments directed to the FDA approval of a phase II human clinical study do not provide support for the enablement since the references specifically teaches that what was performed in vitro does not correlate to in vivo studies. The FDA may have different criteria and motivation for granting various studies which are of no effect in the consideration of the correlation between in vivo and in vitro studies. While the examiner agrees with applicants assertion that the standard of enablement is such that it does not preclude the necessity for some experimentation if routine. However, it is unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention. Accordingly , it would require undue experimentation for a skilled artisan to use the claimed invention.

With respect to the argument directed to different cancers, the amendment to the claim overcomes the argument (page 16-18 of Response filed August 16, 2002).

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 3, 6, 12, 18, 21, 27, 32, 33, 35, 36, and 40 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 3, 6, 12, are indefinite. Claims 3, 6, 12, are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: directed to how to determine whether TAXOL cannot be used to reduce the growth by merely obtaining cells, determining expression of genes in those cells. It appears as though the claim is missing a step directed to treating with TAXOL. Without a step directed to treatment with TAXOL, the claim would not use TAXOL to reduce the growth of cancer cells in any situation where genes are expressed.

Response to Arguments

The response traverses the rejection. The response asserts that it is not necessary to recite a step for exposing the breast cancer cells to TAXOL (page 21 of Response filed August 16, 2002). This argument has been reviewed but is not convincing because the step is essential to the completion of the method. As written, the claims encompass merely taking a sample of breast cells, analyzing the expression of BST-2 and identifying whether TAXOL cannot be used. Without some exposure step or some other means of using TAXOL, the method would not obtain the desired results. The rejection is not directed to detection expression because as noted in the response, numerous means of determining expression level are provided. However, merely determining level of expression on a breast cancer cells does not provide the results of the methods. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

5. No claims allowable.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday- Friday 7:00 a.m. to 4:30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JGoldberg

Jeanine Goldberg
November 2, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600